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a population-based cohort study

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Asthma and risk of myelodysplastic syndromes: a population-based cohort study

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Background: Risk factors for the development of myelodysplastic syndromes (MDS) include age, exposure to ionising radiation, and cytotoxic drug treatment. Recently, asthma also has been suggested as a risk factor for MDS.

Methods: We undertook this nationwide population-based cohort study on patients with a first-time hospital-based asthma diagnosis during 2002–2013 and followed them for the development of MDS/chronic myelomonocytic leukaemia (CMML).

Results: We identified 75 995 patients with incident asthma and no previous MDS/CMML diagnosis. Seventy-eight patients subsequently developed MDS and nine patients developed CMML during 402 892 person-years. The cumulative risks of developing MDS/CMML among asthma patients were 0.02% (95% CI: 0.01–0.04%) and 0.07% (95% CI: 0.05–0.09%) during the first year and the first five years of follow-up, respectively. The standardised incidence ratio of MDS/CMML among asthma patients overall was 1.6 (95% CI: 1.3–2.0) with little variation across subgroups.

Conclusions: Asthma may be a risk factor for the development of MDS/CMML.

Myelodysplastic syndromes (MDS) constitute a group of related clonal hematopoietic disorders (Swerdlow *et al*, 2008). Risk factors for MDS include age, ionising radiation, smoking, occupational exposures, and cytotoxic drugs (Nisse *et al*, 1995; Andersen *et al*, 1998; Bjork *et al*, 2000; Dalamaga *et al*, 2002; Smith *et al*, 2003).

In a cohort of 22 601 women aged 55–59, self-reported asthma in 1997 was associated with a two-fold higher risk of MDS during the median follow-up of 14.8 years (RR = 2.0 (95% confidence interval (CI): 1.0–4.6)). Outcomes were MDS and other incident haematological malignancies identified in the State Health Registry of Iowa (Linabery *et al*, 2014). Although the underlying mechanism is unknown, immune dysregulation in MDS is evident, as some subtypes respond to the treatment with immunosuppressive or immunomodulatory agents (Sauntharajah *et al*, 2003; List *et al*, 2005; Mollgard *et al*, 2011; Duong *et al*, 2012). Some MDS patients also exhibit immune-mediated conditions such as vasculitis (Farah *et al*, 2010). We investigated the association between asthma and MDS/chronic myelomonocytic leukaemia (CMML) in a large cohort of adults.

MATERIALS AND METHODS

We conducted this cohort study using the Danish National Patient Registry (DNPR) and the Civil Registration System (CRS; Schmidt *et al*, 2014; Schmidt *et al*, 2015). The DNPR contains information on all inpatient discharges from hospitals since 1977, and on outpatient clinic and emergency department visits since 1995. The DNPR records patients' civil registration numbers, dates of outpatient visits, hospitalisations, and up to 20 diagnoses coded by physicians according to the WHO's *International Classification of Diseases, Eighth Revision* (ICD-8) until 1993 and *Tenth Revision* (ICD-10) thereafter. We identified all patients aged ⩾18 years with a first-time hospital-based diagnosis of asthma (ICD-10 codes J45–46) in the DNPR during 2002–2013 (Byrjalsen *et al*, 2014) and subsequent diagnoses of MDS or CMML (MDS code: D46, CMML code: C93). We excluded patients whose MDS/CMML diagnosis preceded their asthma diagnosis. The CRS has recorded date of birth, sex, and vital status of all Danish residents since 1968. Follow-up for MDS/CMML began on the date of the asthma

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diagnosis and continued until death, emigration, or 30 November 2013, whichever came first. Inclusion of cohort members began in 2002 after introduction of the WHO classification of MDS and CMML (Swerdlow *et al*, 2008; Dinmohamed *et al*, 2014).

We calculated the risk of MDS/CMML after an asthma diagnosis, treating death as a competing risk. For each calendar year, expected numbers of MDS/CMML in the DNPR were calculated by multiplying the person-years of observation by the appropriate nationwide age-specific and gender-specific incidence rates, with 5-year age groups. Standardised incidence ratios (SIRs) – the ratio of observed numbers of incident cancers to those expected – were used as measures of the relative risk.

We computed 95% CIs for the SIRs based on the assumption that the observed number of cases followed a Poisson distribution. Exact 95% CIs were used when the observed number of MDS/CMML cases was <10; otherwise Byar's approximation was used.

RESULTS

We identified 75 995 patients with incident asthma and no previous diagnosis of MDS or CMML. Their median age was 48.9 years and median follow-up time was 5.0 years (IQR: 2.2–8.2 years). Seventy-eight patients developed MDS and nine patients developed CMML during 402 892 person-years of follow-up. During 1, 5, and 10 years of follow-up, the cumulative risks of developing MDS/CMML for asthma patients were 0.02% (95% CI: 0.01–0.04%), 0.07% (95% CI: 0.05–0.09%), and 0.12% (95% CI: 0.09–0.15%), respectively.

Asthma patients were at increased risk of developing MDS/CMML (SIR 1.6 (95% CI: 1.3–2.0); Table 1). SIR estimates across subgroups were similar (Table 1). When MDS and CMML patients were analysed separately, the SIR for MDS was identical to the overall SIR (1.6 (95% CI: 1.3–2.0)), whereas the SIR for CMML was imprecise (1.4 (95% CI: 0.6–2.6)) due to low numbers. The association was observed in all subgroups, as well as among patients without concurrent COPD (Table 1). As cancer treatment is a risk factor for MDS, we repeated our analyses excluding asthma patients with a previous cancer diagnosis, censoring follow-up if patients developed a cancer diagnosis before MDS/CMML, and also treating both the cancer and death as competing risks. These analyses resulted in virtually identical SIR estimates (data not shown).

DISCUSSION

We found an increased risk of MDS/CMML among patients with an asthma diagnosis. These findings are in line with the study by Linabery *et al* (2014). They reported no association between allergic diseases other than asthma and haematological malignancies. In a review of the previous studies, providing estimates of the association between allergic conditions and haematological myeloid neoplasms, Wang and Diepgen (2005) reported imprecise risk estimates around unity. In a case–control study that specifically included MDS patients and examined self-reported allergic conditions other than asthma, no differences in frequencies of allergies were observed between the MDS patients and their controls (Pekmezovic *et al*, 2006).

The mechanism linking asthma to MDS/CMML remains unknown. Although, epigenetic modifications are common to MDS/CMML and asthma (Yang and Schwartz, 2012; Bravo *et al*, 2014), they are unlikely to explain the association as the hallmark of MDS/CMML is clonal proliferation of neoplastic cells with subsequent epigenetic modifications, whereas asthma is a non-clonal disease.

Most previous studies of allergic conditions and risk of haematological cancers have focused on lymphoid malignancies (Wang and Diepgen, 2005; Turner *et al*, 2006; Melbye *et al*, 2007), with conflicting results. Some studies have found that allergic conditions and specific IgE titres were associated with the decreased risk of lymphoid haematological malignancies, (Wang and Diepgen, 2005), but one study suggested that these findings may be attributed to reverse causality, that is, immunological

Table 1. Observed and expected numbers of patients with myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia (CMML), and standardised incidence ratios (SIRs), among Danish patients diagnosed with asthma during 2002–2013 and followed for MDS and CMML

Patient characteristics (*n*)	Person-years of follow-up among patients with asthma	Asthma patients with MDS or CMML (*n*)	Expected MDS/CMML cases (*n*)	SIR (95% CI)
All (75 995)	402 892	87	54.6	1.6 (1.3–2.0)
Women (47 385)	249 358	47	26.5	1.8 (1.3–2.4)
Men (28 610)	153 533	40	28.1	1.4 (1.0–1.9)
Age at asthma diagnosis (years)				
18–44 (32 712)	192 487	6	2.7	2.2 (0.8–4.9)
45–70 (31 187)	165 779	41	24.2	1.7 (1.2–2.3)
71+ (12 096)	44 626	40	27.7	1.4 (1.0–2.0)
Year of asthma diagnosis				
2002–2007 (38 413)	300 173	60	36.0	1.7 (1.3–2.2)
2008–2013 (37 582)	102 719	27	18.6	1.5 (1.0–2.1)
Follow-up time				
0–1 yr (75 995)	70 645	21	7.7	2.7 (1.7–4.2)
2–5 yrs (66 393)	205 764	35	24.2	1.5 (1.0–2.0)
6–10 yrs (37 644)	116 848	24	19.1	1.3 (0.8–1.9)
>10 yrs (9921)	9634	7	3.6	1.9 (0.8–4.0)
Hospital contact type				
Inpatient admission (26 170)	131 407	41	22.6	1.8 (1.3–2.5)
Outpatient specialist clinic visit only (42 497)	229 960	35	27.4	1.3 (0.9–1.8)
Emergency room only (7328)	41 525	11	4.6	2.4 (1.2–4.3)
Presence of chronic obstructive pulmonary disease (COPD)				
Asthma and COPD (10 829)	44 941	28	13.9	2.0 (1.3–2.9)
Asthma without COPD (65 166)	357 950	59	40.7	1.5 (1.1–1.9)

response to IgE-specific allergens may be compromised among patients with the developing lymphomas (Melbye *et al*, 2007).

Despite its large size, and complete follow-up, our study has limitations. We included only asthma diagnosed in hospital-based settings. Some asthma patients may be diagnosed and followed by their general practitioner without a hospital contact (Hanania *et al*, 2011). However, asthma patients above 65 years of age ($\sim$10% of prevalent asthma cases) are most likely to be referred to hospital-based care (Hanania *et al*, 2011). As the incidence of MDS/CMML increases with age, (Dinmohamed *et al*, 2014) a larger proportion of MDS/CMML patients with a preceding asthma diagnosis would have had a hospital-based asthma diagnosis. During the first year following asthma diagnosis, the SIR estimate for MDS/CMML development was higher than in the following years. Heightened diagnostic effort probably explains part of the association in the short term. However, the increased risk was remarkably persistent many years after an asthma diagnosis.

In the DNPR, the completeness of the asthma diagnosis in conscripts has been found to be 0.44 and the specificity to be 0.98 (Jensen *et al*, 2010). Asthma patients with a hospital referral, however could have a higher risk of MDS/CMML than asthma patients treated only by general practitioners due to potentially, more severe asthma and higher levels of comorbidity. As well, because of our study's registry-based design, we lacked detailed patient-specific information, such as smoking status. Still, when we used a concurrent COPD diagnosis as a proxy for smoking, we observed the association between asthma and MDS/CMML among the asthma patients without COPD.

We conclude that asthma may be a risk factor for the development of MDS/CMML.

AUTHOR CONTRIBUTIONS

HF and HTS conceived the idea for the study. DKF and EH-P performed the statistical analyses. HF wrote the first draft of the manuscript and all authors participated in writing subsequent drafts.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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